Development of a Chimeric Model to Study and Manipulate Human Microglia In Vivo.

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Authors: Jonathan Hasselmann, Morgan A Coburn, Whitney England, Dario X Figueroa Velez, Sepideh Kiani Shabestari, Christina H Tu, Amanda McQuade, Mahshad Kolahdouzan, Karla Echeverria, Christel Claes, Taylor Nakayama, Ricardo Azevedo, Nicole G Coufal, Claudia Z Han, Brian J Cummings, Hayk Davtyan, Christopher K Glass, Luke M Healy, Sunil P Gandhi, Robert C Spitale, Mathew Blurton-Jones

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Public Summary:
iPSC-derived microglia offer a powerful tool to study microglial homeostasis and disease-associated inflammatory responses. Yet, microglia are highly sensitive to their environment, exhibiting transcriptomic deficiencies when kept in isolation from the brain. Furthermore, species-specific genetic variations demonstrate that rodent microglia fail to fully recapitulate the human condition. To address this, we developed an approach to study human microglia within a surrogate brain environment. Transplantation of iPSC-derived hematopoietic-progenitors into the postnatal brain of humanized, immune-deficient mice results in context-dependent differentiation into microglia and other CNS macrophages, acquisition of an ex vivo human microglial gene signature, and responsiveness to both acute and chronic insults. Most notably, transplanted microglia exhibit robust transcriptional responses to Abeta-plaques that only partially overlap with that of murine microglia, revealing new, human-specific Abeta-responsive genes. We therefore have demonstrated that this chimeric model provides a powerful new system to examine the in vivo function of patient-derived and genetically modified microglia.

Scientific Abstract:
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